ISSN 1070-3632, Russian Journal of General Chemistry, 2017, Vol. 87, No. 9, pp. 2111–2114. © Pleiades Publishing, Ltd., 2017.
Original Russian Text © P.L. Padnya, E.E. Bayarashov, O.S. Potrekeeva, I.I. Stoikov, 2017, published in Zhurnal Obshchei Khimii, 2017, Vol. 87, No. 9, pp. 1556–1559.

LETTERS TO THE EDITOR

Dedicated to V. F. Mironov on His 60th Anniversary

Effect of the Alkylidene Spacer and the *p-tert*-Butylthiacalix[4]arene Macrocyclic Platform on the Reactivity of the Hydroxyl Groups in the Acylation Reaction

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Received June 29, 2017

Abstract—A series of cone and 1,3-alternate *p-tert*-butylthiacalix[4]arenes tetrasubstituted at the lower rim simultaneously by the amide, ester, and carboxyl functions were synthesized. The reactivity of the synthesized compounds depends on the length of the alkylidene spacer. The *N*-(hydroxyethyl)amide derivatives do not react with succinic anhydride, whereas the *N*-(3-hydroxypropyl)amide derivatives react to form acylation products.

Keywords: thiacalix[4]arene, succinic anhydride, macrocycles

DOI: 10.1134/S107036321709033X

The thiacalix[4]arene platform works well as an accessible building block for the design of macrocyclic receptors for binding different compounds [1–6]. Tetrasubstituted thiacalix[4]arenes containing at the lower rim simultaneously the amide, ester, and carboxyl functions have found wide application [7–13]. Depending on the length and chemical nature of the spacer between the macrocyclic platform and carboxyl fragments, such compounds can be used as hosts for small biogenic molecules and metal ions or as macromolecular guests such proteins and DNA.

The carboxyl group is a convenient functionality for peptide synthesis [14]. Di- and polycarboxyl derivatives have found application in the synthesis of biodegradable polymers as cross-linking agents for biomacromolecules such as oligo- and polylactides, peptides, and poly(amino acids). In this connection we considered it of interest to develop a synthesis of carboxyl-substituted *p-tert*-butylthiacalix[4]arenes in different conformations (*cone* and *1,3-alternate*), as potential cross-linking reagents. To this end, we chose as starting compounds derivatives of hydroxyl-substituted thiacalix[4]arenes, whose acylation with dicarboxylic acid anhydrides was expected to form polycarboxylated macrocycles with varied length linkers.

First we studied the aminolysis of synthetically available *cone* and *1,3-alternate* thiacalix[4]arene tetraesters **1** and **2** [15] with amino alcohols (2-aminoethanol, 3-aminopropanol). The choice of these amino alcohols was motivated by the fact that they contained different numbers of methylene units between the hydroxyl and amino groups, which could have some impact on the reactivity of the target in the subsequent acylation reactions. *N*-(Hydroxyalkyl)-amides **3** and **4** in the *cone* and *1,3-alternate* con-formations were synthesized by the procedure in [15]. To prepare *N*-(3-hydroxypropyl)amides **5** and **6**, we reacted *cone* and *1,3-alternate* tetraesters **1** and **2** with 3-aminopropanol in toluene–methanol (1 : 1) under reflux for 40 h. *N*-(3-Hydroxypropyl)amides **5** and **6** in the *cone* and *1,3-alternate* conformations were obtained in high yields (Scheme 1).

To prepare tetracarboxylic acids derived from *cone* and *1,3-alternate* thiacalix[4]arenes and containing simultaneously the amide and ester fragments, we reacted compounds **3** and **4** with succinic anhydride in varied conditions (reaction time from 12 to 40 h,